AMENDMENTS

In the claims:

Please amend claim 30 as follows:

30. [THREE TIMES AMENDED] A method of blocking [interfering with] interaction between a bone marrow stromal cell expressing VCAM-1 and a hemopoietic precursor cell which comprises administering an antibody to VCAM-1 in an amount effective to decrease VCAM-1-mediated adhesion between the bone marrow stromal cell and the hemopoietic precursor cell.

REMARKS

I. Preliminary Remarks

For the Examiner's convenience, a copy of all currently pending claims 30-33 as they would appear after entry of this amendment is attached hereto as Exhibit A. The amendments to the claims are requested to place the application in better condition for allowance and/or clarify issues for appeal pursuant to 37 C.F.R. §1.116. Claim 30 is amended to replace the term "interfering" with "blocking." Although Applicants consider both terms to be equivalent in scope, the latter term is used most frequently in the application to describe the action of anti-VCAM-1 antibodies.

II. The Claimed Subject Matter

Claims 30-33 are directed to use of an antibody that binds to vascular cell adhesion molecule-1 (VCAM-1), in methods directly relating to Applicants' discovery that bone marrow stromal cells express VCAM-1 and that VCAM-1 mediates adhesion between bone marrow stromal cells and hemopoietic precursor cells, especially those

bearing the CD34 antigen. A representative embodiment of such an antibody that binds to VCAM-1 and can block VCAM-1-mediated intercellular interactions is the 6G10 monoclonal antibody produced by hybridoma ATCC No. HB 10519.

III. The Outstanding Rejections

Claims 30-33 were rejected under 35 U.S.C. §112, first paragraph, for purportedly lacking written descriptive support in the specification.

Claims 30-33 were rejected under 35 U.S.C. §112, first paragraph as assertedly lacking enablement for the full scope of the claims. It was the Examiner's position that the specification provides insufficient guidance on administration of VCAM-1 specific antibodies in the claimed methods.

Claims 30 and 32-33 were further rejected under 35 U.S.C. §112, first paragraph as assertedly lacking enablement for all VCAM-1-specific antibodies.

IV. Patentability Arguments

A. The Written Description Rejection

Claims 30-33 were rejected under 35 U.S.C. §112, first paragraph, for purportedly lacking written descriptive support in the specification. The Examiner acknowledged that the specification "infer[s] that VCAM-1-VLA-4 interactions occur between hemopoietic cells and stromal elements." However, it was the Examiner's position that the specification only taught the use of anti-VCAM-1 antibody for blocking VCAM-1-mediated adhesion between lymphocytes and either endothelial cells or bone marrow stromal cells, not for blocking VCAM-1-mediated adhesion between hemopoietic cells and bone marrow stromal cells.

Applicants respectfully submit that the specification teaches that anti-VCAM-1 antibodies are useful for interfering with any VCAM-1-mediated adhesion, regardless of the type of cells involved. Submitted herewith in support of Applicants' position is the Second Declaration of Beverly Torok-Storb, Ph.D., Under 37 C.F.R. §1.132.

In paragraphs 4 and 5 of her declaration, Dr. Torok-Storb explains that the specification discloses that VCAM-1 plays a role in the adhesive interaction between hemopoietic precursor cells (which express VLA-4) and bone marrow stromal cells (which express VCAM-1), and that VCAM-1 also mediates adhesive interactions between lymphocytes (which express VLA-4) and activated endothelial cells (which express VCAM-1). These interactions are illustrated in Figures 1 and 2 of her declaration. Dr. Torok-Storb also states that the specification shows that anti-VCAM-1 antibodies such as 6G10 are able to block VCAM-1-mediated adhesion between lymphocytes and activated endothelial cells by up to 80%.

Upon reviewing the application, Dr. Torok-Storb concludes in paragraph 6 that there is no indication that the use of VCAM-1-specific antibodies to interfere with, or block, intercellular adhesive interactions is limited to only some of the disclosed VCAM-1-mediated interactions and not others. On the contrary, she states that one of ordinary skill in the art would understand from reading the application that anti-VCAM-1 antibodies are useful for blocking any VCAM-1-mediated adhesion, regardless of the type of cells involved.

In paragraph 7, Dr. Torok-Storb further disagrees with the Examiner's characterization of page 4, lines 11-16 as referring to blocking adhesion between bone marrow stromal cells (which express VCAM-1) and lymphocytes (which express VLA-4),

but not hemopoietic precursor cells (which also express VLA-4). She concludes that one of ordinary skill in the art as of August 2, 1990 would have clearly understood upon reading the application, particularly the portion at page 4, lines 11-16, that the Applicants taught use of anti-VCAM-1 antibody to inhibit any VCAM-1-mediated adhesive interaction, including the disclosed adhesive interaction between stromal cells and hemopoietic precursor cells (illustrated in Fig. 1). In addition, she notes that one of ordinary skill in the art would have extrapolated results associated with blocking one VLA-4-VCAM-1 interaction, *e.g.* between lymphocytes and endothelial cells (Fig. 2), to another VLA-4-VCAM-1 interaction, *e.g.* between stromal cells and hemopoietic cells (Fig. 1).

Thus, the rejection under 35 U.S.C. §112, first paragraph, for lack of written description may properly be withdrawn in view of the declaratory evidence submitted in support of Applicants' position.

B. The Enablement Rejection

1. Claims 30-33

Claims 30-33 were rejected under 35 U.S.C. §112, first paragraph as assertedly lacking enablement for the full scope of the claims. It was the Examiner's position that the specification provides insufficient guidance on administration of VCAM-1 specific antibodies in the claimed methods. However, Applicants respectfully submit that one of ordinary skill in the art at the time the application was filed could easily have administered VCAM-1 specific antibodies according to the claimed methods. Submitted herewith in support of Applicants' position is the Second Declaration of Thalia Papayannopoulou, M.D., Dr. Sci, Under 37 C.F.R. §1.132.

In paragraph 4 of her declaration, Dr. Papayannopoulou explains that the application teaches that an anti-VCAM-1 antibody, 6G10, binds to bone marrow stromal cells in *in vitro* culture, and that VCAM-1 is implicated in the binding of bone marrow stromal cells to hemopoietic cells. Dr. Papayannopoulou further states that, in light of the knowledge conveyed by the application, one of ordinary skill in the art as of August 2, 1990 would readily have been able to administer an amount of anti-VCAM-1 antibody effective to achieve the therapeutic endpoint, which is the decrease of VCAM-1-mediated adhesion between stroma and hemopoietic precursors, resulting in mobilization of hemopoietic cells. It would have required no more than routine experimentation for the ordinary skilled worker to determine what therapeutic conditions would provide a desired level of measured response.

In paragraphs 5 and 6 of her declaration, Dr. Papayannopoulou references data reported in her previous declaration signed November 30, 1995 (Exhibit B to the response filed December 22, 1995) and data reported in Papayannopoulou *et al., Proc. Nat'l. Acad. Sci (USA), 92*:9647-9651 (1995) (Exhibit 1 to her declaration). She states that these data, obtained with two different antibodies, 6G10 and MK/2, confirm that one of ordinary skill in the art could readily have practiced the claimed methods *in vivo*. Both systemic administration of antibody 6G10 to primates and systemic administration of antibody MK/2 to mice caused release of bone marrow progenitor cells from the bone marrow to the peripheral blood. Dr. Papayannopoulou states that no undue experimentation was involved in either case to achieve the therapeutic endpoint.

Thus, no more than routine effort is required to administer VCAM-1 specific antibodies *in vivo* according to the claimed methods, and this rejection under 35 U.S.C. §112, first paragraph, for lack of enablement may properly be withdrawn.

2. Claims 30 and 32-33

Claims 30 and 32-33 were also rejected under 35 U.S.C. §112, first paragraph, for assertedly lacking enablement for all VCAM-1 specific antibodies. The Examiner's position was that not all VCAM-1 antibodies would bind to bone marrow stroma, based on the notation in Example 5 of the specification that anti-VCAM-1 antibody 4B9 did not significantly bind to stroma. However, one cannot conclude from this that the epitope recognized by 6G10 is the only epitope of VCAM-1 expressed by bone marrow stromal cells. In fact, subsequent publications have demonstrated that antibody 4B9 does in fact bind to bone marrow stroma, and that a number of other anti-VCAM-1 antibodies, such as 14C3, E1/6 and M/K-2, also bind to bone marrow stroma. These publications also show that antibodies 4B9, E1/6 and MK/2 can block adhesion of hemopoietic precursors to bone marrow stromal cells.

Dittel *et al.*, *Blood, 81*:2272-2282 (1993) (Exhibit B hereto) at page 2276, second col., shows that antibody 4B9 does bind to bone marrow stroma and was even able to significantly block B cell precursor adhesion to bone marrow stromal cells (by about 74% after treatment of stromal cells with cytokine IL-1β and by about 52% without cytokine treatment). Liesveld et al., *Blood, 81*:112-121 (1993) (Exhibit C hereto) at page 116, first col. and page 117, Figure 4A, also shows binding of antibody 4B9 to bone marrow stromal cells.

Wilkins *et al.*, *J. Pathol., 177*:295-301 (1995) (Exhibit D hereto) shows that anti-VCAM-1 antibody 14C3 (see Table 1) binds to fibroblastic cells throughout bone marrow stroma. See page 297, first and second cols.

Ryan, *J. Clin. Invest., 88*:995-1004 (1991) (Exhibit E hereto), shows that anti-VCAM-1 antibody E1/6 binds to bone marrow stroma (bone marrow fibroblasts) and

blocks adhesion of B precursor cells to bone marrow fibroblasts. See page 1000, first col., and page 1002, first and second cols.

Jacobsen *et al.*, *Blood, 87*:73-82 (1996) (Exhibit F hereto) states that anti-VCAM-1 antibody M/K-2 binds to bone marrow stromal cells. See page 76, first and second cols. Papayannopoulou *et al.* (1995), *supra* (Exhibit 1 to Dr. Papayannopoulou's declaration) states that administration of antibody MK/2 was "associated with a significant hemopoietic progenitor mobilization . . ." See page 9650, first col.

Thus, Applicants respectfully submit that their showing that at least five different VCAM-1 specific antibodies (6G10, 4B9, 14C3, E1/6 and M/K-2) bind to bone marrow stromal cells, and that at least four of these antibodies (6G10, 4B9, E1/6 and MK/2) block adhesion of hemopoietic precursors to stromal cells, is sufficient to support enablement for all VCAM-1 specific antibodies in the claimed methods.

Although the Examiner was concerned that the antibodies may be "unable to completely block the binding of hemopoietic progenitors" to stromal cells, the Examiner's concern is not relevant to the claims as written, which only recite administration of antibody in an amount effective to "decrease VCAM-1-mediated adhesion." Complete inhibition of adhesion is not required by the claims.

In addition, the Examiner noted that the molecular weight of glycoprotein immunoprecipitated by 6G10 was reportedly 130kD, some 20kD larger than the VCAM-1 found on endothelial cells. The Examiner theorized that this finding "may reflect selective expression by bone marrow stroma of the recently identified VCAM-1 in a form that incorporates an additional seventh domain in its extracellular portion." However, the molecular weight disparity could also be accounted for by variable glycosylation. To the extent that the Examiner appears to propose that human bone marrow stroma selectively

express the seven domain form of VCAM-1 in contrast to the expression of a six domain form of VCAM-1 by endothelial cells, this theory is disproven by a later publication, Cybulsky et al., *Am. J. Pathol., 138*:815-820 (1991) (Exhibit G hereto), which shows that endothelial cells express the seven domain form of VCAM-1 (as well as the six domain form, although the seven domain form appears to predominate). Thus, there is no evidence that bone marrow stroma express a VCAM-1 domain that does not exist on endothelial cells.

The rejection under 35 U.S.C. §112, first paragraph, may properly be withdrawn.

CONCLUSION

In light of the foregoing remarks, it is believed that claims 30-33 are now in condition for allowance, and early notice thereof is solicited.

Respectfully submitted,

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